Association Between Common Carotid Artery Intima-Media Thickness and Proteinuria in Type 2 Diabetic Patients

Ali Momeni,[1] Mohammad Ali Dyani,[2] Morteza Sedehi,[3] Elnaz Ebrahimi[4]

[1]Department of Nephrology, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Department of Radiology, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Department of Epidemiology, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4]Shahrekord University of Medical Sciences, Shahrekord, Iran

Keywords. carotid artery intima-media thickness, proteinuria, diabetes mellitus

Introduction. Proteinuria is the most reliable marker of diabetic nephropathy and an index of atherosclerosis and cardiovascular mortality in diabetic patients. In addition, common carotid artery intima-media thickness (CIMT) is a sensitive marker of early atherosclerosis and cardiovascular risk. The aim of this study was to evaluate the association between proteinuria and CIMT in type 2 diabetic patients.

Materials and Methods. In a cross-sectional study, 154 patients with type 2 diabetes mellitus were enrolled. The CIMT was measured for all of the patients by one researcher. The 24-hour urine protein was measured using trichloroacetic acid method.

Results. A total of 154 type 2 diabetic patients were enrolled with a mean diabetes mellitus duration of 8.91 ± 6.99 years (95 women and 55 men). The mean urinary protein in the patients was 294.70 ± 525.85 mg/24 h. The mean CIMT in all of the patients was 0.84 ± 0.19 mm, and it was greater in the men than in the women (P = .03). The CIMT significantly correlated with patients' age (P < .001), systolic blood pressure (P < .001), and urinary protein excretion (P = .001). There was a marginal positive correlation between diabetes mellitus duration and the CIMT (P = .049).

Conclusions. This study showed a significant association between CIMT, as a sensitive marker of macrovascular complication of diabetes mellitus, and proteinuria as an important index of microvascular complication of the disease.

IJKD 2015;9:311-5
www.ijkd.org

Original Paper

INTRODUCTION

Diabetes mellitus (DM) is associated with aggressive vascular disease, and atherosclerosis is a leading cause of morbidity and mortality in diabetic patients. In addition, DM is the most common cause of renal damage and end-stage renal disease. The earliest sign of diabetic nephropathy is microalbuminuria which can lead to macroalbuminuria and progressive kidney function impairment.[1] The reported prevalence of microalbuminuria among patients with type 2 DM 10 years after diagnosis ranges from 25% to 40%, which is more common among Asians. Microalbuminuria develops in 25% to 40% of type 2 diabetic patients after 10 years of disease initiation. Albuminuria is regarded as a marker of generalized endothelial dysfunction and has been a strong predictor of vascular atherosclerosis, which can be presented as ischemic heart disease, cerebrovascular accident, or peripheral vascular disease.[2] Based on the positive associations between the common carotid artery intima-media thickness (CIMT) and cardiovascular risk factors, CIMT is a well-accepted index of subclinical cardiovascular disease.[3]

Diabetic atherosclerosis can be detected by the measurement of the CIMT. The CIMT has been used to predict cardiovascular outcomes in diabetic patients.[4] The easy applicability and the

noninvasive nature of B-mode ultrasonography make it suitable for serving as a surrogate endpoint for measuring the atherosclerotic burden in individuals with cardiovascular risk factors.[5] The mean CIMT values are different based on the methods of ultrasonographic evaluation (transversal, longitudinal anterolateral, or longitudinal posterolateral).[6] In diabetic patients, the C IMT is significantly greater than that of in nondiabetic individuals.[7] Increases in the CIMT may be associated with an increased risk of myocardial infarction and stroke in aged patients without a history of cardiovascular disease.[8] The mean CIMT was reported as a reliable marker of risk in the case of ischemic stroke in type 2 diabetic patients and could be used as a simple noninvasive screening test for the assessment of atherosclerosis in these patients.[9] The mean CIMT may be associated with age, systolic blood pressure, smoking, the ratio of low- to high-density lipoprotein cholesterol, mean glycosylated hemoglobin value, and urinary albumin excretion rate.[10] In type 2 diabetic patients, significant predictors of the CIMT progression were reported as microalbuminuria, high age, male sex, smoking, and high systolic blood pressure.[11]

Moreover, proteinuria is the most reliable marker of diabetic nephropathy and an index of atherosclerosis and cardiovascular mortality in diabetic patients. On the other hand, the CIMT is a sensitive marker of early carotid atherosclerosis; thus, measurement of the CIMT by ultrasonography can be used to assess the cardiovascular risk and to determine indications for better management of DM and intensified insulin treatment. The aim of our study was to evaluate the relationship between proteinuria and CIMT as two valuable noninvasive methods for early detection of microvascular and macrovascular complications of DM.

MATERIALS AND METHODS

In a cross-sectional study, 154 patients with type 2 DM who were referred to the nephrology clinic of Hajar Hospital, Shahrekord, Iran, were enrolled. Medical history of all patients was taken and physical examination was performed in each person. Exclusion criteria were patients with age of less than 40 years, patients' nonadherence during the study, history of congestive heart failure, hypothyroidism, and other causes of transient proteinuria such as febrile illness or urinary tract infection during the past 2 weeks. Informed consent was obtained from all of the participants.

Measurement of the CIMT was done in the patients at the 2-cm distance of the common carotid bifurcation, by the same sonographist, in the supine position, using a Doppler ultrasonography device (Siemens G50, Germany) with linear multifrequencies of 7.5- to 10-MHz probe). Demographic criteria such as age, duration of DM, body mass index (BMI), systolic and diastolic blood pressure, and laboratory results including fasting blood glucose, hemoglobin A1c, blood urea nitrogen, and serum creatinine were checked and recorded in patients' file. Laboratory tests were conducted by means of biotechnical instruments (BT 3000, Germany). In all patients, 24-hour urine protein was measured by trichloroacetic acid method, using a photometer (ECOM-E G125, Eppendorf, Germany). Blood was taken from all patients after 10 hours of fasting.

The data were collected and analyzed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). The *t* test and the chi-square test were used for comparisons and the Pearson Correlation coefficients were calculated for assessment of the relationship between numeric variables.

RESULTS

A total of 154 type 2 diabetic patients, including 95 women and 55 men were enrolled. The mean ages of were 58.22 ± 9.47 years for the women and 62.24 ± 9.74 years for the men. The patients had a mean DM duration of 8.91 ± 6.99 years (Table 1).

Table 1. Demographic and Clinical Data of the Participants

Variables	Mean Value
Age, y	59.65 ± 9.74
Body mass index, kg/m^2	29.29 ± 4.42
Systolic blood pressure, mm Hg	13.91 ± 19.93
Diastolic blood pressure, mm Hg	83.73 ± 13.68
Total cholesterol, mg/dL	178.38 ± 46.55
High-density lipoprotein cholesterol, mg/dL	47.17 ± 19.82
Low-density lipoprotein cholesterol, mg/dL	96.05 ± 43.11
Triglyceride, mg/dL	199.61 ± 106.68
Fasting blood glucose, mg/dL	139.84 ± 50.83
Blood urea nitrogen, mg/dL	23.72 ± 11.25
Serum creatinine, mg/dL	1.28 ± 0.62
Hemoglobin A1c, %	7.20 ± 1.26
Duration of diabetes, y	8.91 ± 6.99
Carotid intima-media thickness, mm	0.84 ± 0.19

Table 2. Comparisons Between the Men and the Women With Diabetes Mellitus

Variable	Female	Male	*P*
Body mass index, kg/m^2	30.21 ± 4.31	27.61 ± 4.13	.001
Duration of diabetes, y	7.68 ± 5.57	11.10 ± 8.62	.003
Total cholesterol, mg/dL	186.37 ± 46.67	163.98 ± 43.10	.004
Fasting blood glucose, mg/dL	147.87 ± 51.10	125.36 ± 47.41	.008
Blood urea nitrogen, mg/dL	21.45 ± 9.28	27.80 ± 13.24	.001
Serum creatinine, mg/dL	1.10 ± 0.48	1.59 ± 0.70	.001
Serum protein, mg/dL	200.31 ± 507.51	464.60 ± 519.90	.003
Carotid intima-media thickness, mm	0.82 ± 0.16	0.89 ± 0.22	.03

Serum cholesterol, fasting blood glucose, and BMI values were higher in the women; however, serum creatinine and blood urea nitrogen levels were higher and duration of DM was longer in the men (Table 2). The mean urinary protein in the patients was 294.70 ± 525.85 mg/24 h (200 ± 500 mg/24 h and 464 ± 519 mg/24 h, in the women and the men, respectively; $P < .001$).

The mean CIMT in all of the patients was 0.84 ± 0.19 mm, and the mean CIMT was greater in the men than in the women (0.82 ± 0.16 mm versus 0.89 ± 0.22 mm, respectively; $P = .03$). There was a weak positive correlation between DM duration and CIMT ($P = .049$). The CIMT significantly correlated with patients' age and systolic blood pressure ($P < .001$; Table 3). The mean urinary protein in the patients significantly correlated with the CIMT ($P = .001$).

DISCUSSION

Our study showed a significant association between the CIMT and proteinuria in type 2 diabetic patients. We also found a relationship between the CIMT and patient's age, blood urea nitrogen, serum creatinine, and systolic blood pressure. Normal value of the CIMT is reported to be 0.6 mm to .08 mm based on age; therefore, a CIMT greater than 0.9 mm to 1 mm has been suggested as indicative of atherosclerosis that may increase the risk of cardiovascular disease.[12] In the present study, the mean CIMT was 0.85 ± 0.19 mm, which was greater in the male than the female patients.

Table 3. Association Between Carotid Intima-Media Thickness and Patients' Parameters

Variables	Correlation Coefficient	*P*
Age	0.280	< .001
Age at disease onset	0.150	.06
Duration of disease	0.150	.049
Body mass index	0.006	.93
Systolic blood pressure	0.310	< .001
Diastolic blood pressure	0.130	.10
Hemoglobin A1c	0.025	.75
24-hour urine protein	0.260	.001
Serum creatinine	0.200	.01
Blood urea nitrogen	0.160	.03
Fasting blood glucose	0.050	.50
High-density lipoprotein cholesterol	-0.080	.32
Low-density lipoprotein cholesterol	0.035	.66
Triglyceride	0.079	.32
Total cholesterol	-0.001	.87

The CIMT increases with age. Juonala and colleagues[13] reported that the IMT were increased 5.7 ± 0.4 μm per year, but in a study by Tanaka and colleagues[14] on 129 healthy normotensive, nonobese, nonsmoker men aged 18 to 77 years, no significant increase was observed in carotid artery lumen diameter by increasing age. They concluded that the discrepancy between the results was likely due to the differences in health status among participants in each study.

Chronic kidney disease and azotemia have been identified as a risk factor of atherosclerosis and ischemic heart disease.[15] Tanaka and colleagues[16] studied on 1003 patients older than 50 years and found that the estimated GFR was adversely correlated with the CIMT. In addition, Gentile[17] showed an independent relationship between impaired creatinine concentration and common carotid plaques in a study on 310 women. The CIMT was greater in patients with a serum creatinine greater than 1 mg/dL compared to those with a lower concentration. Juonala and coworkers[13] showed that there are a negative correlation between the CIMT and glomerular filtration rate, but there was no negative correlation between the CIMT and the stage of diabetic nephropathy.

There are some studies on the association between the CIMT and hypertension; for example,

Manios and coworkers[18] reported a higher CIMT in prehypertensive patients than normotensive individuals and a higher CIMT in hypertensive patients than prehypertensive ones. Sander and colleagues[19] evaluated 286 patients older than 55 years and concluded that the CIMT was significantly higher in the patients with increased systolic blood pressure variability. Similarly, we found an association between the CIMT and age, systolic blood pressure, and serum creatinine. In a study on 338 diabetic patients,[20] a significant relationship was observed between the CIMT and age, duration of DM, and hypertension. Di Bello and colleagues[21] investigated on 198 asymptomatic hypertensive patients and showed a significant association between the CIMT and severity of hypertension. In a study on 240 elderly Japanese subjects, Oishi and colleagues[22] concluded that the mean systolic blood pressure and the mean pulse pressure but not diastolic blood pressure were associated with the CIMT. The CIMT is greater in white-coat and grade 1 hypertensive patients than that of normotensive subjects.[23] Controversy in the results of the abovementioned studies may be due to the number of the patients or racial parameters.

Yokoyama and colleagues[24] found a positive correlation between CIMT and BMI and serum triglyceride in a study on 536 type 2 diabetic patients, which did not match with our results. However, Joseph and coworkers[11] found this association only in patients with a BMI greater than 30 kg/m^2. Also, different results were found in men and women regarding proteinuria, BMI, serum cholesterol, and duration of DM. These discrepancies may be due to the differences between the number of male and female patients.

There were a few studies about the association between CIMT and proteinuria, most of which were consistent with our results. For example, Zhang and colleagues[2] found a significant correlation between the CIMT and microalbuminuria in 250 type 2 diabetic patients. Taniwaki and coworkers[25] found that IMT was not different between the two groups of normoalbuminuric and microalbuminuric patients. Tanaka and colleagues[16] found that the CIMT had a correlation with proteinuria. Finally, Leena and associates[26] showed a significant correlation between the CIMT and microalbuminuria in a study on 450 diabetic patients.

CONCLUSIONS

This study showed a significant association between the CIMT as a sensitive marker of systemic atherosclerosis and macrovascular complication of DM with proteinuria as an important index of nephropathy and microvascular complication of DM. The CIMT may be used as a marker for both microvascular and macrovascular complications of DM. Interpretation of our results though are limited by the small sample size and lack of urinary albumin measurement. We suggest doing further studies with larger sample sizes to confirm this relationship.

ACKNOWLEDGMENTS

This study was the result of a research project (no 986) approved by the Research Committee of the Deputy of Research and Technology affiliated with Shahrekord University of Medical Sciences. The authors acknowledge the personnel at the Department of Radiology in Kashani Hospital and Hajar Hospital for their support.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Momeni A, Behradmanesh MS, Kheiri S, Horestani MK. Evaluation of spironolactone plus hydrochlorothiazide in reducing proteinuria in type 2 diabetic nephropathy. J Renin Angiotensin Aldosterone Syst. 2013.
2. Zhang YH, Gao Y, Mao X, Shang J, Su BL. Assessment of carotid atherosclerosis in type 2 diabetes mellitus patients with microalbuminuria by high-frequency ultrasonography. Int J Endocrinol. 2013;2013:819584.
3. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. Stroke. 1992;23:1752-60.
4. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB, Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med. 2011;365:213-21.
5. George JM, Bhat R, Pai KM, S A, Jeganathan J. The carotid intima media thickness: a predictor of the clincal coronary events. J Clin Diagn Res. 2013;7:1082-5.
6. Casella IB, Presti C, Porta RM, Sabbag CR, Bosch MA, Yamazaki Y. A practical protocol to measure common carotid artery intima-media thickness. Clinics (Sao Paulo). 2008;63:515-20.
7. Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, et al. Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. Diabetes Care. 1999;22:333-8.
8. Nichols WW, Pepine CJ, O'Rourke MF. Carotid-artery

intima and media thickness as a risk factor for myocardial infarction and stroke. N Engl J Med. 1999;340:1762-3.

9. Kota SK, Mahapatra GB, Naveed S, Tripathy PR, Jammula S, Modi KD. Carotid intima media thickness in type 2 diabetes mellitus with ischemic stroke. Indian J Endocrinol Metab. 2013;17:716-22.
10. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med. 2003;348:2294-303.
11. Polak JF, Backlund JY, Cleary PA, et al. Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes. 2011;60:607-13.
12. Lim TK, Lim E, Dwivedi G, Kooner J, Senior R. Normal value of carotid intima-media thickness--a surrogate marker of atherosclerosis: quantitative assessment by B-mode carotid ultrasound. J Am Soc Echocardiogr. 2008;21:112-6.
13. Juonala M, Kahonen M, Laitinen T, et al. Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: the cardiovascular risk in Young Finns Study. Eur Heart J. 2008;29:1198-206.
14. Tanaka H, Dinenno FA, Monahan KD, DeSouza CA, Seals DR. Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. Arterioscler Thromb Vasc Biol. 2001;21:82-7.
15. Gentile M, Panico S, Mattiello A, et al. Plasma creatinine levels, estimated glomerular filtration rate and carotid intima media thickness in middle-aged women: A population based cohort study. Nutr Metab Cardiovasc Dis. 2013.
16. Tanaka M, Abe Y, Furukado S, et al. Chronic kidney disease and carotid atherosclerosis. J Stroke Cerebrovasc Dis. 2012;21:47-51.
17. Gentile M, Panico S, Mattiello A, et al. Plasma creatinine levels, estimated glomerular filtration rate and carotid intima media thickness in middle-aged women: A population based cohort study. Nutr Metab Cardiovasc Dis. 2014;24:677-80.
18. Manios E, Tsivgoulis G, Koroboki E, et al. Impact of prehypertension on common carotid artery intima-media thickness and left ventricular mass. Stroke. 2009;40: 1515-8.
19. Sander D, Kukla C, Klingelhofer J, Winbeck K, Conrad B. Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: A 3-year follow-up study. Circulation. 2000;102:1536-41.
20. Ito H, Komatsu Y, Mifune M, et al. The estimated GFR, but not the stage of diabetic nephropathy graded by the urinary albumin excretion, is associated with the carotid intima-media thickness in patients with type 2 diabetes mellitus: a cross-sectional study. Cardiovasc Diabetol. 2010;9:18.
21. Di Bello V, Carerj S, Perticone F, et al. Carotid intima-media thickness in asymptomatic patients with arterial hypertension without clinical cardiovascular disease: relation with left ventricular geometry and mass and coexisting risk factors. Angiology. 2009;60:705-13.
22. Oishi E, Kagiyama S, Ohmori S, et al. Association of systolic blood pressure and pulse pressure with carotid intima thickness in elderly Japanese patients. Clin Exp Hypertens. 2013;35:273-8.
23. Puato M, Palatini P, Zanardo M, et al. Increase in carotid intima-media thickness in grade I hypertensive subjects: white-coat versus sustained hypertension. Hypertension. 2008;51:1300-5.
24. Yokoyama H, Kuramitsu M, Kanno S, Tada J, Yokota Y, Kamikawa F. Relationship between metabolic syndrome components and vascular properties in Japanese type 2 diabetic patients without cardiovascular disease or nephropathy. Diabetes Res Clin Pract. 2007;75:200-6.
25. Taniwaki H, Nishizawa Y, Kawagishi T, et al. Decrease in glomerular filtration rate in Japanese patients with type 2 diabetes is linked to atherosclerosis. Diabetes Care. 1998;21:1848-55.
26. Mykkanen L, Zaccaro DJ, O'Leary DH, Howard G, Robbins DC, Haffner SM. Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects. The Insulin Resistance Atherosclerosis Study (IRAS). Stroke. 1997;28:1710-6.

Correspondence to:
Mohammad Ali Dyani, MD
Hajar Hospital, Shahrekord, Iran
Tel: +98 381 222 0016
Fax: +98 381 334 9506
E-mail: madayani@yahoo.com

Received January 2015
Accepted January 2015